Tetrahedron Letters, Vol. 34, No. 43, pp. 6837-6840, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Multipoint Recognition of Carboxylates by Neutral Hosts in Non-polar Solvents

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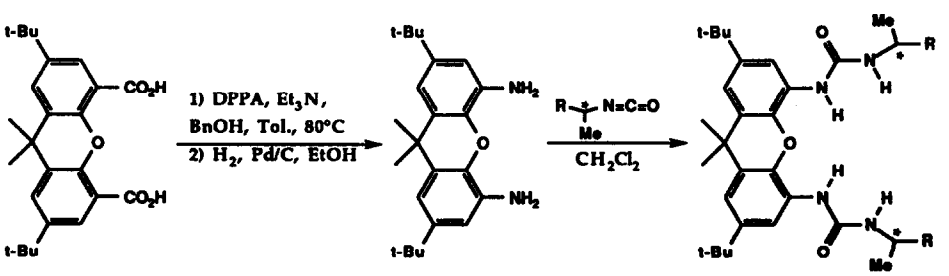
Abstract: A neutral molecular receptor of carboxylates has been developed using the convergent ureas as the binding site. The data indicate that chelation of the carboxylates occurs by the urea hydrogens. Asymmetric centers in the host are shown to influence the nmr spectrum of a guest bound within.

Molecular recognition of anions through charge-charge interactions is well developed[1] yet the binding of carboxylates with neutral hosts has seen little success. A neutral carboxylate receptor offers the advantage of uses in hydrophobic settings such as in membranes for transport. Asymmetric elements of the host, properly positioned, provide the additional possibility of enantioselection of guests. The ureas **3** and **4** were developed in this regard: they exploit the recently demonstrated ability of mono ureas to bind carboxylates,[2] allow for multipoint hydrogen bonding, present an asymmetric microenvironment, and offer rapid, modular synthetic combinations.

Scheme



1 **2** **3** R=Phenyl
4 R=1-Naphthyl

Hosts 3 and 4 (Scheme) were prepared from xanthenedicarboxylic acid[3] (1) via Curtius rearrangement using diphenylphosphorylazide (DPPA)[4] and benzyl alcohol followed by hydrogenolysis of the resulting carbamate to the diamine 2. Bis ureas 3 and 4 were obtained by fusing diamine 2 to the appropriate isocyanates.

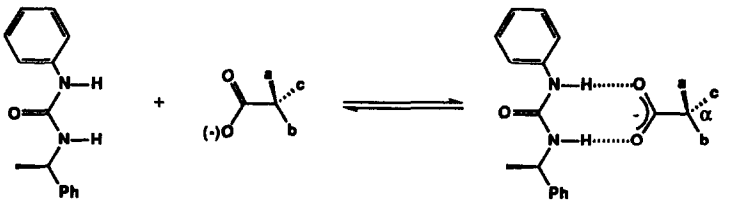


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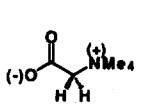
Figure 1

The carboxylate affinity of receptor 3 was investigated using ^{1}H NMR. In a titration with tetramethylammonium benzoate in $CDCl_3$ the urea N-H signals of host 3 shift > 3 ppm downfield, suggesting the ureas are actively involved in the binding. The large association constant (K_a=2x10^5) for this system compared to mono urea 5 (K_a=400) indicates both ureas cooperate in the binding of the carboxylate by 3. In addition, a Job Plot[5] showed a maximum at the 1:1 complex. Thus, chelation plays a critical role in complexation. For systems with large association constants, aggregation can often suppress observed host-guest interactions, this was determined to be negligible for the case at hand ($K_{a(dimer)}$=18).



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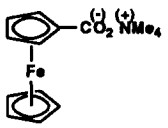

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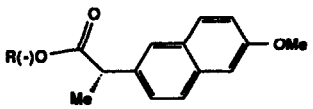
The position of the α-carbon of a carboxylate with respect to its usual recognition surfaces (syn lone pairs) represents a unique difficulty in the recognition of chiral carboxylic acids (Figure 1). Hosts 3 and 4 are attractive in this respect since they may overcome this through chelation; the asymmetric elements in the host are placed nearer to the α-carbon of the carboxylate guest. Encouraging results were obtained using guests with enantiotopic protons and bis urea 3. In solid/liquid extractions, a $CDCl_3$ solution of 3 effectively solubilized 1.3 equivalents of the otherwise insoluble betaine 6. The ^{1}H NMR spectrum of this 1:1 complex showed the methylene protons of the betaine to be non-equivalent, δ 3.35 (d, J=15.6, 1H) δ 3.15 (d, J=15.6, 1H). These enantiotopic protons became diastereotopic when they were bound within the chiral cleft. Experiments with the mono urea congener 5 show that only 0.3 equivalents of betaine were dissolved and no differentiation of the methylene protons occurred. This behavior was also observed in the proximal ring of ferrocencecarboxylic acid 7 upon addition of its ammonium salt to host 3.

The ability of host **3** to distinguish enantiomers was also examined. Naproxen **9** in $CDCl_3$ was chosen for initial studies in this regard, but the inability of ^1H NMR titration procedures to accurately determine association constants > 10^4 prompted a change in the solvent. Methanol, a more competitive hydrogen bonding medium, lowered the association constants into a reliably measurable range (Table 1). In this solvent enantioselectivity is quite modest.[7]

Table 1. Association Constants for Asymmetric Guests

Host	Guest	Solvent	Ka(M^{-1}) (ref.6)
3 (R,R)	**8**	$CDCl_3$	$3.5x10^5$
3 (S,S)	**8**	$CDCl_3$	$1.6x10^5$
3 (R,R)	**8**	CD_3OD	71
3 (S,S)	**8**	CD_3OD	77
3 (R,R)	**9**	CD_3OD	130
3 (S,S)	**9**	CD_3OD	150
4 (R,R)	**9**	CD_3OD	160
4 (S,S)	**9**	CD_3OD	110



8 R=$Et_4N(+)$
9 R=$Me_4N(+)$

The subtleties in the binding of naproxen with the enantiomers of both hosts **3** and **4** were probed by modeling and NOE experiments. Computer modeling (MacroModel V3.5X,[8] using the AMBER* force field) in conjunction with NOE data predicts the complex will adopt a conformation where the ureas are rotated slightly out of the plane of the xanthene (Figure 2). This forces the carboxylate to approach from one of the faces of the xanthene, while the asymmetric centers are directed above the opposite face. This orientation minimizes the steric interactions of asymmetric elements of both host and guest to a disappointing degree.

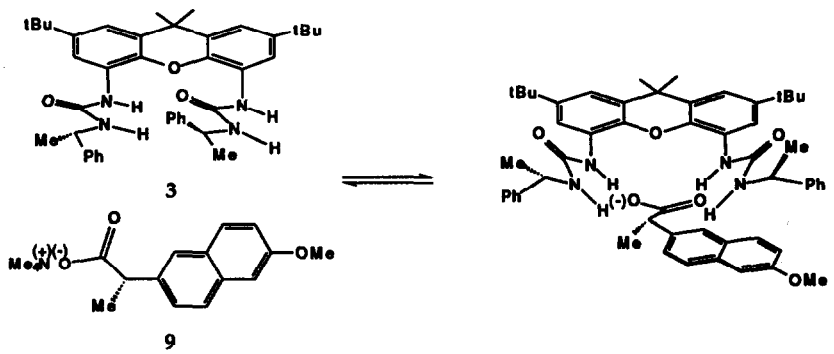


Figure 2

In conclusion, neutral, organic soluble receptors for carboxylates are described and their synthetic accessibility offers access to a variety of peripheral functional groups. Although the chiral

microenvironments of hosts **3** and **4** provided little in the way of enantioselection, their influence on prochiral guests was established.

Acknowledgments: We wish to thank the Biotechnology Process Engineering Center under the direction of Dr. Daniel I. C. Wang and acknowledge the support from the National Institutes of Health Interdepartmental Biotechnology Training Grant Program NIH-5-T32-GM08834 and NIH Studies in Molecular Recognition GM27932 which made this research possible.

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(Received in USA 17 May 1993; accepted 11 August 1993)